

## Living Evidence Profile

### Examining what is known about the emergence, transmission and spectrum of the burden of disease of avian influenza A (H5Nx) subtypes

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#### Context

- Avian influenza A (H5Nx) viruses have been reported globally, leading to large outbreaks in poultry, wild birds and mammals.
- Recent H5 viruses (clades 2.3.4.4b and 2.3.2.1c) have emerged or re-emerged, causing concern on the potential transmission and spectrum of the burden of disease in humans.
- This living evidence profile (LEP) aims to identify the current state of evidence and knowledge gaps from existing evidence syntheses related to the emergence, transmission and spectrum of the burden of disease in humans of avian influenza as a first step towards informing prevention and mitigation interventions.
- This version of the LEP was focused only on identifying existing evidence syntheses and did not include a jurisdictional scan, but expansions in scope may be made in future to include single studies and/or a jurisdictional scan to provide more detailed insights to support ongoing work towards informing prevention and mitigation interventions.

#### + Global evidence drawn upon



Evidence syntheses selected based on relevance, quality and recency of search

#### \* Additional notable features

Prepared in three business days using an 'all hands-on deck' approach

#### Questions

- What is known about the emergence, transmission (including spillover potential) and spectrum of the burden of disease in humans of avian influenza A (H5Nx) subtypes currently circulating and emerging?

#### High-level summary of key findings

- We found 16 evidence syntheses that provided insights about four of the domains prioritized to assess in the LEP (biology, epidemiology, diagnosis, and clinical presentation of avian influenza A (H5Nx)), but that seldomly provided insights specific to the other domains of interest (emergence, transmission and spectrum of the burden of disease in humans of influenza A (H5Nx)).
- The majority of the evidence syntheses described H5Nx subtypes in general, but they did not explicitly report on the circulating clades (2.3.4.4b and 2.3.2.1c) or other emerging subtypes.
- In general, H5Nx subtypes have circulated in different regions of the world (e.g., China, Egypt, North America, Western Pacific), with most transmissions among birds.
- Movement of birds, humans and fomites play a role in influenza A transmission among birds and birds to humans during poultry production, but evidence is conflicting.
  - While there has been transmission reported through case reports, the evidence syntheses identified indicate, based on two older studies, that backyard farms play a limited role in highly pathogenic avian influenza

(HPAI) transmission where reproduction numbers were found to be below one for transmission between backyard farms and between backyard and commercial farms.

- The collection of environmental samples appears to be a promising technique for surveillance and detection.
- We identified limited information on the burden of disease in humans.
- Within the identified literature, key gaps were described about poultry production and networks, sample techniques, contextual factors and parameters that influence transmission and risks across species, and approaches to developing optimal avian influenza surveillance programs.
- Additional next steps should focus on efforts to fill gaps in the literature such as generation of evidence syntheses on the biology of circulating clades, susceptibility and transmission parameters, diagnosis and clinical presentation across species (birds, non-human mammals, humans), and clear descriptions of priority population groups.

## Framework to organize what we looked for

- Biology
  - Circulating clades
    - 2.3.4.4b
    - 2.3.2.1c
    - Other (if new subtypes identified as having emerged)
  - Genomic changes and impacts on:
    - Infectivity/transmission
    - Pathogenicity
    - Virulence/disease severity
    - Mammalian adaptation
    - Antiviral susceptibility
  - Virological characteristics
    - Infectivity/transmission (i.e., likelihood to infect a host)

## Box 1: Approach and supporting materials

At the beginning of each living evidence profile and throughout its development, we engage a subject matter expert, who helps us to scope the question and ensures relevant context is taken into account in the summary of the evidence.

We identified evidence addressing the question by searching ACCESSSS, Health Systems Evidence, Health Evidence and [PubMed](#) for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses) and protocols for evidence syntheses. These searches were last conducted on 18 December 2023 and were not limited by publication date except in PubMed, which was limited to literature published from the last five years (2019 onwards). We also included evidence identified from internal searches provided by the Public Health Agency of Canada (PHAC) that were conducted for literature published since October 2022 with the last search conducted on 13 December 2023. The search strategies used are included in Appendix 1. In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents. Note, that the timing, frequency and scope of future updates of this LEP will be determined in collaboration with the requestor and that, while single studies and jurisdictional scans have not yet been prioritized for inclusion in this LEP, they may be included in future enhanced versions.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using AMSTAR. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial or governance arrangements within health systems or to broader social systems.

A separate appendix document includes:

- 1) methodological details (Appendix 1)
- 2) details from evidence documents organized by circulating clade (Appendix 2)
- 3) details about each identified synthesis (Appendix 3)
- 4) documents that were excluded in the final stages of review (Appendix 4).

This living evidence profile was prepared in the equivalent of three days of a ‘full court press’ by all involved staff.

- Pathogenicity (i.e., ability to cause disease)
  - Virulence/disease severity
- Epidemiology (including transmission)
  - Route of transmission
    - Bird to non-human mammal
    - Non-human mammal to mammal (including development of a non-human mammal reservoir)
    - Bird/non-human mammal to human (i.e., zoonotic transmission)
    - Environmental viral load (e.g., avian and mammalian viral shedding)
    - Human to human
  - Reported cases and other epidemiological indicators of avian influenza A(H5Nx) (e.g., prevalence, case fatality rates, geographic distribution)
  - Susceptibility and transmission parameters
    - Incubation period
    - Clinical illness period
    - Latent period
    - Infectious period
    - Virus shedding
- Diagnosis
  - Molecular methods for rapid detection
  - Serological diagnostics (e.g., self-testing, point-of-care diagnostics)
- Clinical presentation
  - Immunological characteristics
    - Innate
    - Adaptive
    - Antigen/antibody and cellular immune responses
- Priority populations
  - Groups at higher risk of exposure
    - Working on a commercial poultry farm (e.g., producer, processing plant worker, poultry culler)
    - Working with non-commercial or backyard flocks
    - Breeding and handling birds (e.g., dealer, breeder of exotics, falconry, racing pigeons)
    - Hunting and trapping wild birds and mammals (e.g., Indigenous harvesters)
    - Working with live or recently killed poultry (e.g., butcher)
    - Working with wild birds and/or mammals for healthcare, research and conservation (e.g., veterinarians, laboratory workers, researchers, biologists, wildlife rehabilitators, persons permitted to perform bird branding, capturing, sampling, removal, restoration)
    - Working with non-human mammals that commonly eat wild birds
    - Working or visiting live bird or mammal markets
    - Working with or caretaking of animals that regularly interact with wild birds (e.g., caretakers, pets, guardian dogs, hunting dogs, mink farmer)
    - Working in healthcare settings and other contacts of cases (if human-to-human transmission starts)
  - Other equity considerations

## What we found

We found 16 evidence syntheses that provided insights about four of the domains prioritized to assess in the LEP (biology, epidemiology, diagnosis, and clinical presentation of avian influenza A (H5Nx)), but that seldomly provided insights specific to the other domains of interest (emergence, transmission and spectrum of the burden of disease in humans of influenza A (H5Nx)). Many evidence documents were excluded (but are listed in Appendix 4), largely because they were literature reviews without an explicit search strategy. The methodological details of the

living evidence profile can be found in Box 1 and Appendix 1. We describe below the gaps and findings from the evidence syntheses with additional details about each of the included evidence syntheses provided in Appendix 3.

## **Gaps in existing evidence syntheses**

We found several gaps in existing evidence syntheses. Most of the evidence syntheses described H5Nx subtypes in general, but they did not explicitly describe the circulating clades (2.3.4.4b and 2.3.2.1c) or other emerging subtypes. Overall, we found limited evidence about the biology, epidemiology, diagnosis, clinical presentation in general or specific to priority populations or across H5Nx subtypes and clades. Some reasons could be due to the focus on evidence syntheses for this version, the indexing of avian influenza A literature in the bibliographic databases (e.g., mostly literature reviews with no methods section), and limited detailed descriptions within the identified evidence syntheses. Within the identified literature, authors described key evidence gaps about poultry production and networks, sample techniques, contextual factors and parameters that influence transmission and risks across species, and approaches to developing optimal avian influenza surveillance programs.(1-16)

## **What existing evidence syntheses tell us about the emergence, transmission and spectrum of the burden of disease in humans of influenza A**

### *General H5Nx subtypes*

The identified evidence syntheses described the biology, epidemiology, diagnosis and clinical presentation of avian influenza A (H5Nx). In terms of biology (virological characteristics), a medium-quality evidence synthesis reported on transmission dynamics largely focusing on individual birds as the epidemiological unit. The authors suggested that most HPAI transmission between poultry farms occurred within a short to medium distance range to each other regardless of subtype or geographical location. The authors reported a reproduction number ranging from 0.03–15.7 for between-farm transmission in poultry of H5N1.(12) A low-quality evidence synthesis found that HPAI virus shedding was higher than that of low pathogenicity avian influenza virus (LPAI). For the introduction routes of HPAI viruses, intranasal or intraconal routes resulted in no difference in shedding compared to infection by contact. Overall, virus shedding levels among poultry largely depend on the introduction routes (e.g., intranasal, aerosol, oropharyngeal).(7)

Related to epidemiology, eight evidence syntheses described the prevalence, route of transmission and susceptibility parameters among birds, non-human mammals, and humans. Three low-quality evidence syntheses described the prevalence in birds from different regions around the world. In Sub-Saharan Africa, the authors reported an overall 3.0% prevalence, with H5N1 being the most frequently observed, followed by H5N2 and H5N8 among both wild and domestic birds (particularly in chickens and ducks).(10) According to the authors, Indigenous African bird species and migratory water birds from Eurasia keep avian influenza viruses in circulation. Further, they indicated that H5N1 HPAI viruses were widespread in this region due to being a major wintering destination for migratory water birds.(10) In China, it was found that waterfowl were considered the most important transmitters of avian influenza viruses (including the H5Nx subtypes), however the prevalence in wild birds varied by region.(3) One low-quality evidence synthesis reported a combined global prevalence of 1.6% of H5N8 among birds.(1) We found one low-quality evidence synthesis that described the prevalence of H5N1 in humans. In Egypt, it was found that most H5N1 human-infection cases were among children, younger adults and those with direct exposure to poultry.(14) Two medium-quality and two low-quality evidence syntheses described other routes of transmission and susceptibility parameters. One evidence synthesis found the movement of birds, humans and fomites all play a role in transmitting HPAI viruses among birds and between humans and birds during poultry production (e.g., live bird movements between farms, chick movements from hatchery, bird pick-up to slaughter for broiler production, feed delivery, egg collection, human movement such as contact from veterinarians or farm workers).(8) Another evidence synthesis described the risk of interspecies transmission from backyard farms that involve both domestic poultry and swine.(2) However, one evidence synthesis found that the role of backyard farms in transmission was

minimal.(12) Finally, authors in another evidence synthesis highlighted the importance for studies to contextualize the species and subtypes to have a better understanding of transmission and risk.(11)

Related to the diagnosis of avian influenza A (H5Nx), three evidence syntheses (one low-quality and two medium-quality) indicated that promising techniques largely involve sample collections from live birds at markets and farms (e.g., swabs and serology), dead birds (e.g., swabs and/or organ samples) and the environment (e.g., feces, mud, feeding sources, feathers and air and surfaces likely contaminated with viruses such as cages, chopping boards, defeathering machines, trucks and boots).(5; 9; 13)

For clinical presentation, one medium-quality evidence synthesis indicated that LPAI H5 typically cause mild clinical symptoms among poultry. However, HPAI viruses like H5N2, H5N6, H5N8 was described to cause severe morbidity and mortality in poultry.(12)

#### *Clade 2.3.4.4b*

We identified limited insights about clade 2.3.4.4b from evidence syntheses. Relevant evidence identified is primarily based on epidemiological findings in China, the Western Pacific Region, and North America. In terms of epidemiology, one medium-quality evidence synthesis found that the overall seroprevalence of H5N1 infection among humans was 2.45% in China, with a higher seroprevalence in Central China (7.3%).(15) A low-quality evidence synthesis indicated that the risk of zoonotic transmission is low in Western Pacific Region, despite changes in primary subtypes and frequency of reported cases.(16) Another low-quality evidence synthesis found that this particular clade was found among wild birds in Alaska, and the authors concluded that these wild birds likely contributed to outbreaks among wild and domestic birds in Canada and the United States in recent years.(6)

We also identified one low-quality evidence synthesis that found that people with poultry exposures (e.g., poultry workers and cullers) had higher seroprevalence of H5N1 antibodies than non-poultry exposed people. There were low frequencies of antibodies detected among close contacts of confirmed H5N1 cases.(4)

#### *Clade 2.3.2.1c*

We found very limited information on clade 2.3.2.1c in the identified evidence syntheses. This particular clade was mentioned briefly in a low-quality evidence synthesis, where they described the low risk of zoonotic transmission in the Western Pacific Region as low.(16)

### **Next steps**

Additional next steps should focus on efforts to fill gaps in the literature, which include:

- evidence syntheses on the biology (genomic changes, virological characteristics) with clear descriptions of the circulating clades, including different characteristics among circulating clades
- evidence syntheses on susceptibility and transmission parameters
- evidence syntheses on diagnosis and clinical presentation of avian influenza A (H5Nx) categorized by birds, non-human mammals and humans
- evidence syntheses with clear descriptions of the population groups, particularly among those at higher risk of exposure.

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